Sciences, DHHS, and by a grant from The Jane Coffin Childs Memorial Fund for Medical Research.

Registry No. 11, 90-33-5; 11 acetate, 2747-05-9; 12, 14003-96-4; 13a, 86290-39-3; 13b, 86290-40-6; 14a, 86290-41-7; 14b, 86290-42-8; 15a, 86290-43-9; 15b, 1616-54-2; 16, 86290-44-0; 17, 86290-45-1; 18a, 86290-46-2; 18b, 86290-47-3; 19, 86290-48-4; 20, 86290-49-5; 21, 86290-50-8; 23, 93-35-6; 23 acetate, 10387-49-2; 24, 2555-29-5; 25, 6748-68-1; 27, 6835-55-8; 28a, 86290-51-9; 29a, 86290-52-0; 29b, 72939-36-7; 30a, 86290-53-1; 30b, 86290-54-2; 31a, 86290-55-3; 31b, 86290-56-4; 32, 86290-57-5; 33, 55136-72-6; 34, 86290-58-6; 35, 86290-59-7; 36, 86290-60-0; 38, 86290-61-1; 39, 86290-62-2; 41, 86290-63-3; 42, 86290-64-4; 44, 14256-46-3; 45, 86290-65-5; 46, 86290-66-6; 47, 86290-67-7; 48, 86290-68-8; 49, 86308-27-2; 50, 86290-69-9; 51, 86290-70-2; 52, 86290-71-3; 53, 86290-72-4; 54, 86290-73-5; 55, 86290-74-6; 56, 86290-75-7; 57, 86290-76-8; 58, 86290-77-9; 59, 86290-78-0; 60, 86290-79-1; 2,3-dichloro-1-propene, 78-88-6; neopentyl glycol, 126-30-7.

Halogenation of Pyrimidine 6-*O*-Cyclonucleosides

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Pyrimidine 6-*O*-cyclonucleosides (**1**, **5**, **8**, **11**, and **15**) were treated with halogen (Cl_2, Br_2, or I_2) or *N*-halosuccinimide to afford the corresponding 5-monohalogeno derivatives (**2**, **6**, **9**, and **12**), together with a novel type of 6,2′:6,5′-, 6,3′:6,5′-, and 6,2′:6,3′-dianhydro-5,5-dihalo-5,6-dihydro-6,6-dihydroxyuracil nucleosides (**3**, **7**, **13**, and **16**). The structure of each dihalogeno compound was elucidated on the basis of elemental analysis, mass spectrum, and proton magnetic resonance spectrum. The ease of an additional cyclization of pyrimidine 6-*O*-cyclonucleoside depends on the close proximity of the nucleophilic hydroxyl group in the sugar moiety to C-6 in the pyrimidine base. The mass spectra of these halogeno compounds were also discussed.

Halopyrimidine nucleosides provide useful pathways to a wide variety of interesting nucleoside analogues.[1] In addition, some of them have potent medicinal properties; 5-iododeoxyuridine[2] and 1-(tetrahydro-2-furanyl)-5-fluorouracil[3] have been used clinically as antiviral and antitumor agents, respectively. As part of our program concerned with the synthesis and biological test of pyrimidine 6-*O*-cyclonucleosides,[4] we report halogenation of these nucleosides, which led to monohalogeno derivatives, together with a novel type of dihalogeno nucleosides possessing two oxygen bridges between the base and the sugar.

I. Bromination of Pyrimidine 6-*O*-Cyclonucleosides

Reaction of 6,2′-*O*-cyclouridine[5] (**1a**) with bromine water[6] at room temperature afforded two products. A major compound was isolated from the reaction mixture in 46% yield, which had a molecular formula $C_9H_8N_2O_6Br_2$ on the basis of elemental analysis and mass spectrum (MS). It had no ultraviolet (UV) absorption maximum in the B_{2U} region, showing the loss of the 5,6 double bond of the pyrimidine base. The proton magnetic resonance (^1H NMR) spectrum (Me_2SO-d_6) revealed that the two C-5′ protons were shifted downfield[7] compared with those of **1a** and upfield[8] compared with those of 8 and could be analyzed as the AB part of an ABX spin system due to the coupling with C-4′ proton.[7] The C-2′ proton was shifted upfield[8] compared with that of **1a**. The structure was thus established as 6,2′:6,5′-dianhydro-1-(β-D-arabinofuranosyl)-5,5-dibromo-5,6-dihydro-6,6-dihydroxyuracil (**3a**). This is the first example of a novel type of cyclonucleoside with two oxygen bridges between the base and the sugar, starting from the mono-*O*-cyclonucleoside.[9] A minor compound was isolated by successive treatment of the mother liquor in 32% yield, which was identified as the 5-bromo derivative **2a** on the basis of elemental analysis ($C_9H_9N_2O_6Br \cdot {}^1/_2H_2O$) and MS ($m/z$ 320, 322 (M^+)). A plausible mechanism for the formation of **3a** is as follows. An additional bromination at the 5-position of the intermediate **2a** would be initiated by an electrophilic attack of the bromonium cation on the 5,6 double bond of the pyrimidine base, followed by nucleophilic attack of the 5′-hydroxyl group on the electron-deficient 6-position (trans addition), which would result in the intramolecular 6,5′-*O*-cyclization. This interpretation receives support from the fact that the reaction of **2a** with bromine water leads to the formation of **3a**. The ease of intramolecular nucleophilic attack of the 5′-hydroxyl group on C-6 might depend on the close proximity of the two groups. Reaction of **1a** with a small excess of *N*-bromosuccinimide (NBS) in dimethylformamide (DMF) at room temperature provided **3a** as a sole product in 52% yield. Reaction of 6,2′-*O*-cyclocytidine (**1b**) with bromine water did not afford the corresponding dibromo derivative (**4**), but **3a**. Such a deamination would be due to susceptibility of the intermediate **4** to deamination.[10]

A similar bromination of 6,3′-*O*-cyclouridine (**5**) with bromine water gave two compounds in yields of 5.3% and 75%, respectively, which were assigned 5-bromo-6,3′-*O*-cyclouridine (**6a**) and 6,3′:6,5′-dianhydro-5,5-dibromo-5,6-dihydro-6,6-dihydroxy-1-(β-D-xylofuranosyl)uracil (**7a**), respectively, based on the elemental analyses, the ^1H NMR spectra, and the mass spectra. The structure of **7a** was

(1) Kochetkov, N. K., Budovskii, E. I., Ed. "Organic Chemistry of Nucleic Acids"; Plenum Press: New York, 1972; Part B, p 275.
(2) Maxwell, E. *Am. J. Opthal.* **1963**, *56*, 571.
(3) Valdivieso, M.; Bodey, G. P.; Gottlieb, J. A.; Freireich, E. J. *Cancer Res.* **1976**, *36*, 1821.
(4) Maruyama, T.; Sato, S.; Honjo, M. *Chem. Pharm. Bull.* **1982**, *30*, 2688.
(5) Abbreviation for 6,2′-anhydro-1-(β-D-arabinofuranosyl)-6-hydroxyluracil. Other similar abbreviations are used in this paper.
(6) Fukuhara, T. K.; Visser, D. W. *J. Biol. Chem.* **1951**, *190*, 95.
(7) (a) Manor, P. C.; Saenger, W.; Davies, D. B.; Jankowski, K.; Rabczenko, A. *Biochem. Biophys. Acta* **1974**, *340*, 472. (b) Ikehara, M.; Ogiso, Y. *Chem. Pharm. Bull.* **1975**, *23*, 1114.
(8) The shift would be due to the decrease in anisotropy based on the disappearance of 5,6 double bond of the pyrimidine base.
(9) The synthesis of a similar type of cyclonucleoside was reported, but the method is different from that of ours in terms of the acetalation of C-2 carbonyl by the 5′,6′-diol system in a hexafuranosylcytosine derivative: David, S.; de Sennyey, G. *J. Chem. Soc., Chem. Commun.* **1981**, 780.
(10) (a) Chang, P. K. *J. Org. Chem.* **1965**, *30*, 3913. (b) Honjo, M.; Furukawa, Y.; Nishikawa, M.; Kamiya, K.; Yoshioka, Y. *Chem. Pharm. Bull.* **1967**, *15*, 1076.

0022-3263/83/1948-2719$01.50/0

Table I. 90-MHz Proton Chemical Shifts (ppm) of 5,5-Dihalo Di-O-cyclo Compounds in Me_2SO-d_6

compd	H-1′	H-2′	H-3′	H-4′	H-5′a	H-5′b	N^3-H	other
8	6.15 (s)	4.29 (d)		4.36 (m)	4.53 (dd)	3.92 (dd)	11.24 (br s)	
3a	6.27 (d)	4.81 (d)	4.24 (s)	4.34 (m)	4.10 (dd)	3.59 (d)	11.75 (br s)	5.66 (br s, 3′-OH)
3b	6.21 (d)	4.78 (dd)	4.23 (m)	4.31 (m)	4.10 (dd)	3.59 (dd)	11.77 (br s)	5.60 (br s, 3′-OH)
7a	5.83 (s)	3.99 (m)	4.83 (d)	4.73 (m)	4.01 (dd)	3.77 (d)	11.50 (br s)	5.82 (d, 2′-OH)
7b	5.86 (s)	4.02 (s)	4.86 (m)	4.78 (m)	4.08 (dd)	3.86 (d)	11.70 (br s)	5.85 (br s, 2′-OH)
11	6.03 (d)	5.27 (t)	4.42 (m)	4.06 (m)	3.56 (m)	3.25 (m)	10.81 (m)	5.61 (d, 3′-OH) 4.95 (d, H-5) 4.61 (t, 5′-OH)
13a	6.08 (d)	4.80 (t)	4.18 (m)	4.30 (m)	4.10 (dd)	3.72 (dd)	11.45 (br s)	5.63 (d, 3′-OH)
13b	6.07 (d)	4.80 (t)	4.18 (m)	4.27 (m)	4.10 (dd)	3.73 (dd)	11.65 (br s)	5.66 (br s, 3′-OH)
15	6.06 (d)	5.29 (t)	4.33 (m)	4.23 (m)	0.97 (d)		11.00 (br s)	5.67 (d, 3′-OH) 5.00 (d, H-5)
16	5.75–5.95 (m)		4.67 (t)	4.38 (d)	1.12 (m)		11.51 (br s)	

Table II. First-Order Coupling Constant of 5,5-Di-O-halo Di-O-cyclo Compounds (Hz)

compd	$J_{1',2'}$	$J_{2',3'}$	$J_{3',4'}$	$J_{4',5'a}$	$J_{4',5'b}$	$J_{5'a,5'b}$
8	0	0	0	1.5	0.5	13.0
3a	5.0	0	*a*	3.5	1.0	13.0
3b	5.0	1.5	*a*	3.0	2.0	13.5
7a	0.5	0.5	*a*	2.0	0.5	11.0
7b	0.5	*a*	*a*	2.0	0	11.0
11	5.0	5.0	5.5	4.5	6.0	13.5
13a	4.5	4.5	*a*	1.5	2.0	13.5
13b	4.0	4.0	*a*	1.5	2.0	13.0
15	5.5	5.5	*a*	6.0		
16	*a*	3.0	3.0	6.5		

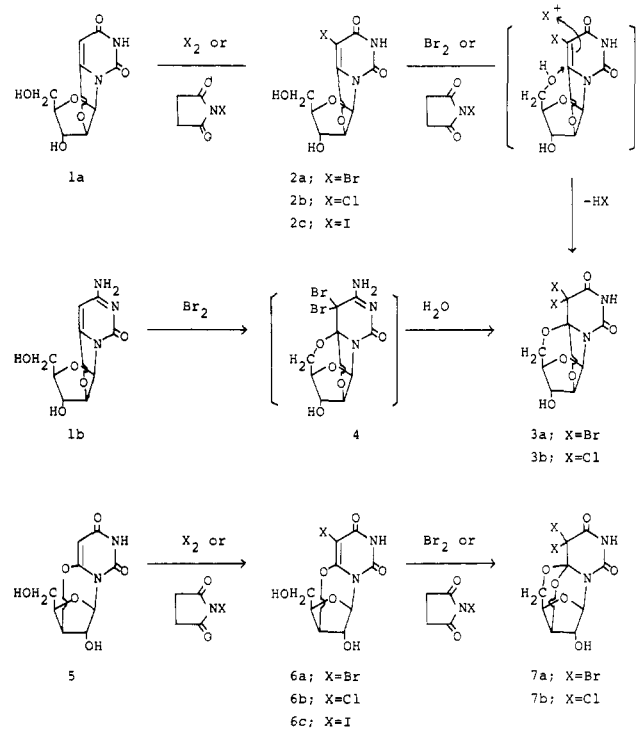
[a] Unresolved.

also conclusively determined by X-ray crystallography.[11] The higher yield of **7a** over **3a** could be explained by the closer proximity of the 5′-hydroxyl group to C-6 in **7a** than that in **3a**, as was demonstrated by a Corey–Pauling–Koltun (CPK) model (Chart I, Tables I and II).

Reaction of 6,5′-O-cyclouridine (**8**) with bromine water yielded, in addition to 5-bromo derivative **9**, a product showing a lower R_f value by thin-layer chromatography (TLC) [$CHCl_3$–EtOH (4:1)]. The compound might arise from fission of the 6,5′-O-cyclo bond, which is labile to acid.[4] Therefore, **8** was allowed to react with NBS to obtain **9a** in a good yield. Bromination of **8** afforded neither **3a** nor **7a**. These data show that an additional O-cyclization requires an "upward" hydroxyl group in the sugar moiety.

An attempt was made to synthesize 6,2′:6,3′-dianhydro-5,5-dibromo-5,6-dihydro-6,6-dihydroxy-1-(β-D-lyxofuranosyl)uracil. Iodination of 1-(β-D-lyxofuranosyl)uracil (**10a**) gave the 5-iodo derivative (**10b**). Treatment of **10b** with sodium methoxide yielded 6,2′-anhydro-6-hydroxy-1-(β-D-lyxofuranosyl)uracil (**11**). The structure of **11** was confirmed by elemental analysis and ^1H NMR spectrum (downfield shift of C-2′ proton signal). Reaction of **11** with bromine water provided two compounds. A minor product was proved to be 5-bromo derivative (**12**) by elemental analysis. A major product was assigned the 6,2′:6,5′-dianhydro-5,5-dibromo-5,6-dihydro-6,6-dihydroxy-1-(β-D-lyxofuranosyl)uracil structure (**13a**) by ^1H NMR spectrum and elemental analysis. A CPK model of **11** shows a shorter distance between the 5′-hydroxyl group and C-6 than that between the 3′-hydroxyl group and C-6, because C-3′ is in the exo conformation owing to the 6,2′-O-cyclic linkage. In order to remove a participation of the 5′-hydroxyl group of **11**, the 5′-deoxy derivative (**15**) of **11** was prepared by treatment of 1-(5′-deoxy-β-D-lyxofuranosyl)-5-iodouracil (**14b**) with sodium methoxide. Reaction of **15** with bromine water afforded a main product, whose migration on TLC was similar to that of the monobromo compound. However, treatment of **15** with NBS provided a main product showing a R_f value similar to that of the dibromo compound. White crystalline materials were isolated from the reaction mixture in 38% yield. The structure of the product was established as 6,2′:6,3′-dianhydro-5,5-dibromo-5,6-dihydro-6,6-dihydroxy-1-(5′-deoxy-β-D-lyxofuranosyl)uracil (**16**) by elemental analysis and ^1H NMR spectroscopy (disappearance of the 3′-hydroxyl signal and the downfield shift of C-3′ proton signal). The greater difficulty for the additional 3′-O-cyclization of **15** to **16** may be due to the decreased access of the "upward" 3′-hydroxyl group to C-6, owing to the exo conformation of C-3′ (Chart II).

Chart I



II. Chlorination and Iodination of Pyrimidine 6-O-Cyclonucleosides

Reaction of **1a** with *N*-chlorosuccinimide (NCS) in DMF at room temperature under an atmosphere of argon gas afforded the 5-chloro derivative **2b** in 23% yield. Further reaction at 50 °C yielded 5,5-dichloro derivative **3b** in 95% yield. A similar reaction of **5** (or **8**) with NCS provided the corresponding 5-chloro derivative **6b** (or **9b**). Prolongation of the reaction of **5** and **11** with NCS afforded 5,5-dichloro compounds, **7b** and **13b**, respectively.

(11) Wada, Y.; Kamiya, K.; Maruyama, T.; Honjo, M., manuscript in preparation.

Table III. Selected Ions from the Mass Spectra (70 eV) of 5-Halo-6-O-cyclouracil Nucleosides (Percent Relative Abundance)

compd	M+	M − 29	M − 31	M − 59	M − 74	M − 75	M − 88	M − 89	M − 113	M − 114	M − 132
2a	100.0		16.6		37.6		(~37.9)			11.0	20.6
2b	100.0		18.2	6.5	48.9		(~38.0)			14.8	26.6
2c	100.0		4.7		1.6	18.2	1.8	7.2	1.1	8.2	10.1
6a	67.5		4.7		17.8		(~9.9)		31.7	56.0	8.8
6b	100.0		10.5	6.0	31.0	4.5	(~17.0)		40.0	66.1	16.9
6c	53.8		1.5			5.0			11.7	100.0	1.5
9a	51.3	10.2		18.6			35.2	10.6	100.0	99.3	68.7
9b	34.1	6.0		12.2			25.8	8.0	73.2	60.4	53.6
9c	61.6	6.3		10.7			22.8	5.4	77.6	100.0	48.8
11	92.2		29.9	21.1	100.0		17.6	84.3	6.7	6.9	55.9
12	16.2		1.5		5.2		(~10.1)			7.9	5.7

Table IV. Selected Ions from the Mass Spectra (70 eV) of 5,5-Dihalo Di-O-cyclo Compounds (Percent Relative Abundance)

compd	M+ + 1	a	b	c	d	e	f	g
3a	0.6		5.6	68.7	39.8	4.5	6.8	2.8
3b	2.0			4.8	5.0	9.0	100.0	23.8
7a		7.3	5.5	3.0	3.5	6.0		
7b		4.8		1.2	2.2			
13a			9.5	37.0	17.1	2.9	6.2	1.1
13b	2.3			2.2	3.3	5.8	100.0	18.8

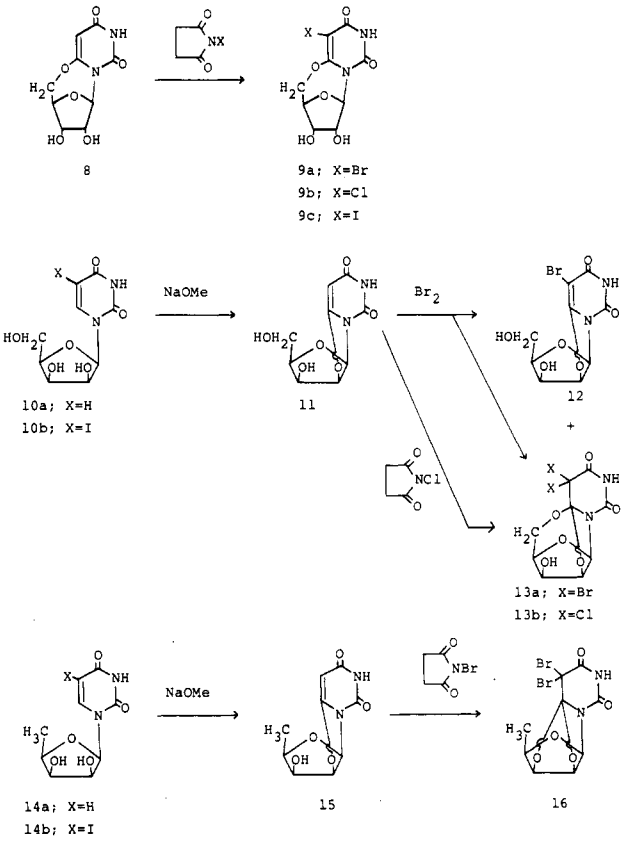
Reaction of **1a** (or **5**) with iodine in the presence of iodic acid or with *N*-iodosuccinimide (NIS) at room temperature gave the corresponding 5-iodo derivative **2c** (or **6c**) in a good yield, but the 5,5-diiodo compound could not be isolated. Treatment of **8** with NIS brought about a similar result (**9c**).

III. Mass Spectra of Halogeno Compounds Derived from Pyrimidine 6-*O*-Cyclonucleosides

The spectra of the bromo compounds provide useful information for their identification, because of a characteristic relative abundance of the bromo isotope. Intensive molecular ion peaks (M^+) were detected in all 5-bromo derivatives other than **13a**. The latter compound was susceptible to dehalogenation to show a low abundance of M^+ fragment followed by a high abundance of bromo cation and hydrogen bromide fragments. The spectra of 5-bromo-6,2′- (**2a** and **12**) and 6,3′-*O*-cycloisomers (**6a**) demonstrated the same main fragment ion peaks, such as M − 31 formed by simple loss of 5′-CH_2OH[4,12] and M − 74 produced by further loss of HNCO from the base moiety.[4] The fragmentation ion peak of M − 74 was not detected in the spectrum of 5-bromo-6,5′-*O*-cycloisomer (**9a**). The spectra of **2a**, **6a**, and **12** exposed M − 89, regardless of disturbance from the neighboring fragment ion peaks, and showed M − 132 which is presumed to arise by the successive retro-Diels–Alder expulsion of HNCO[13] in the base moiety. Intensive fragment ion peaks of M − 113 and M − 114 were observed in the spectra of 5-halo-6,5′- (**9a** and **9c**) and 6,3′-*O*-cycloisomers (**6a** and **6c**), supporting the view that these compounds are susceptible to alkyl–O fission (Table III).[4]

6,2′:6,5′-Dianhydro-5,5-dihalo-5,6-dihydro-6,6-dihydroxyuracil nucleosides afforded characteristic spectra, which did not show M^+, but $M^+ + 1$ ion peaks. One type of their fragmentation pattern (type A) involved cleavage of the bond between oxygen and C-6, as was shown in the 5,5-dibromo derivatives (**3a** and **13a**). The other type of fragmentation pattern (type B) was that the fragments retained the bond between oxygen and C-6 as was shown in the 5,5-dichloro derivatives (**3b** and **13b**). Fragmentation process in the type A consisted of the successive elimination of bromine, 5′-CH_2O, and HNCO (a → b → c → d). The structure of c assigned to M − Br − 30 was in agreement with that derived from **2a** by the elimination of 5′-CH_2OH. The fragmentation process in the type B (a → e → f → g) would be similar to that which has been shown in the fragmentation pattern of pyrimidine 6,5′-*O*-cyclonucleosides.[14] The type of fragmentation pattern might be governed by the ease of elimination of halogeno ion (Chart III, Table IV).

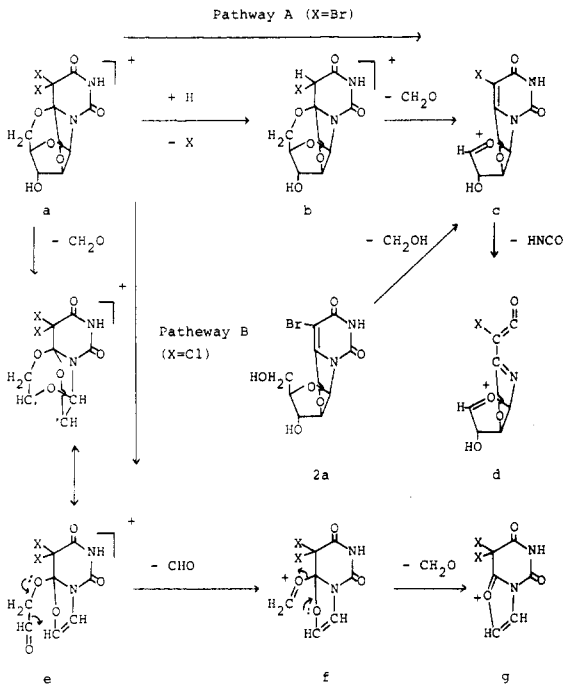
Chart II



6,3′:6,5′-Dianhydro-5,5-dihalo-5,6-dihydro-6,6-dihydroxyuracil nucleosides afforded M^+ ion peaks. The spectra showed a low abundance of such fragments as were displayed in those of the corresponding 6,2′:6,5′-dianhydro counterparts, a low abundance of some fragments that

(12) Tsuboyama, S.; McClosky, J. A. *J. Org. Chem.* **1972**, *37*, 166.
(13) Puzo, G.; Schram, K. H.; Liehr, J. G.; McClosky, J. A. *J. Org. Chem.* **1978**, *43*, 767.
(14) Lovett, E. G.; Lipkin, D. *J. Am. Chem. Soc.* **1973**, *95*, 2312.

Chart III



would be derived from 5-halo- or 5,5-dihalouracil, and a high abundance of m/z 84–86, 68, and 69, formed by the elimination of HNCO from 6-hydroxyuracil and uracil. These facts indicate that the electron-impact-induced reaction of the dihalogeno derivatives **7a** and **7b** would result in decomposition of the base moiety without retention of the intermediate fragment ions.

Experimental Section

All melting points were determined on a Yanagimoto micromelting point apparatus (hot stage type) and are uncorrected. The UV spectra were recorded with a Shimadzu UV-190 digital spectrometer. The ^{1}H NMR spectra were recorded with a Hitachi R-42 (90 MHz) spectrometer in Me_2SO-d_6 with tetramethylsilane as an internal standard. Mass spectra were measured with a Shimadzu-LKB 9000B spectrometer in 10-mm path-length cells. Paper chromatography (PC) was carried out on Toyo filter paper no. 51 by the ascending method with use of the following solvents: A, BuOH–AcOH–H_2O (5:2:3); B, BuOH–H_2O (84:16). TLC was carried out on plates (2 × 10 cm) coated with Wakogel B-5 including fluorescent indicator F_{254} (Merck). Each compound with its recorded R_f value showed a single UV absorbing spot by TLC.

6,2′:6,5′-Dianhydro-1-(β-D-arabinofuranosyl)-5,5-dibromo-5,6-dihydro-6,6-dihydroxyuracil (3a) and 5-Bromo-6,2′-*O*-cyclouridine (2a). i. To 6,2′-*O*-cyclouridine[4] (**1a**; 309 mg, 1.28 mmol) was added Br_2–water dropwise with shaking until the color of bromine was not discharged. The reaction mixture was filtered to give white needles (**3a**; 236 mg, 46%): mp 224–226 °C; TLC [$CHCl_3$–EtOH (9:1)] R_f 0.42.

Anal. Calcd for $C_9H_8N_2O_6Br_2$: C, 27.03; H, 2.02; N, 7.00; Br, 39.95. Found: C, 27.05; H, 2.14; N, 7.23; Br, 39.82.

The filtrate was evaporated to dryness and the residue was triturated with EtOH to deposit white needles (**2a**; 131 mg, 32%): mp 259–261 °C; TLC [$CHCl_3$–EtOH (4:1)] R_f 0.39; UV (0.1 N HCl) λ_{max} 266.5 nm (ε 13 400); UV (H_2O, neutral) λ_{max} 266 nm (ε 13 200); UV (0.1 N NaOH) λ_{max} 265 nm (ε 9800).

Anal. Calcd for $C_9H_9N_2O_6Br \cdot {}^1/_2H_2O$: C, 32.75; H, 3.05; N, 8.49. Found: C, 32.35; H, 2.73; N, 8.17.

ii. To a solution of **1a** (1.00 g, 4.13 mmol) in DMF (10 mL) was added NBS (1.77 g, 2.4 equiv). The mixture was stirred at room temperature for 1 h and the solvent was evaporated in vacuo. The residue was triturated with water to yield a precipitate. The crude product was recrystallized from water to give **3a** (850 mg, 52%): mp 223–225 °C.

iii. 6,2′-*O*-Cyclocytidine[4] (**1b**; 300 mg, 1.24 mmol) was treated with Br_2–water to give **3a** (148 mg, 30%): mp 224–226 °C.

Anal. Calcd for $C_9H_8N_2O_6Br_2$: C, 27.03; H, 2.02; N, 7.00. Found: C, 27.09; H, 1.89; N, 6.68.

6,3′:6,5′-Dianhydro-5,5-dibromo-5,6-dihydro-6,6-dihydroxy-1-(β-D-xylofuranosyl)uracil (7a) and 5-Bromo-6,3′-*O*-cyclouridine (6a). 6,3′-*O*-Cyclouridine[4] (**5**; 500 mg, 2.07 mmol) was treated with Br_2–water in a similar manner to that described in the proceeding section to yield colorless prisms (**7a**; 618 mg, 75%): mp 209–211 °C; TLC [$CHCl_3$–EtOH (9:1)] R_f 0.49.

Anal. Calcd for $C_9H_8N_2O_6Br_2$: C, 27.03; H, 2.02; N, 7.00. Found: C, 27.39; H, 1.82; N, 6.95.

The filtrate was evaporated to dryness and the residue was triturated with water to deposit colorless needles (**6a**; 35 mg, 5.3%): mp >300 °C; UV (0.05 N HCl) λ_{max} 274 nm; UV (H_2O, neutral) λ_{max} 274 nm; UV (0.05 N NaOH) λ_{max} 273.5 nm.

5-Iodo-1-(β-D-lyxofuranosyl)uracil (10b). To a solution of 1-(β-D-lyxofuranosyl)uracil[15] (**10a**; 4.00 g, 16.4 mmol) in 1 N HNO_3 (40 mL) was added I_2 (6.00 g) and $CHCl_3$ (20 mL). The mixture was heated under reflux with stirring for 1.5 h. After cooling, the solid was collected and washed thoroughly with ether. Recrystallization of the product from EtOH–water yielded colorless prisms (5.22 g, 86%): mp 214–215.5 °C; TLC [$CHCl_3$–EtOH (4:1)] R_f 0.39; UV (0.1 N HCl) λ_{max} 287 nm (ε 7700); UV (H_2O, neutral) λ_{max} 287 nm (ε 7800); UV (0.1 N NaOH) λ_{max} 280 nm (ε 6100).

Anal. Calcd for $C_9H_{11}N_2O_6$: C, 29.21; H, 3.00; N, 7.57. Found: C, 29.59; H, 2.96; N, 7.31.

6,2′-Anhydro-6-hydroxy-1-(β-D-lyxofuranosyl)uracil (11). A solution of **10b** (5.22 g, 14.1 mmol) in 1 N NaOMe (70 mL) was heated under reflux for 3 h. After cooling, the mixture was evaporated to dryness and the residue was dissolved in water (70 mL). The aqueous solution was treated successively with Amberlite IR 120B (H^+; 2.5 × 40 cm) and Amberlite IRA 400 (AcO^-; 2.7 × 13 cm). The effluent and washings were combined and concentrated to deposit white prisms (2.94 g, 85%): mp 242–244 °C; TLC [$CHCl_3$–EtOH (4:1)] R_f 0.13; UV (0.1 N HCl) λ_{max} 252 nm (ε 16 900); UV (H_2O, neutral) λ_{max} 251 nm (ε 16 600); UV (0.1 N NaOH) λ_{max} 254 nm (ε 12 300).

Anal. Calcd for $C_9H_{10}N_2O_6$: C, 44.63; H, 4.16; N, 11.57. Found: C, 44.89; H, 4.27; N, 11.54.

6,2′:6,5′-Dianhydro-5,5-dibromo-5,6-dihydro-6,6-dihydroxy-1-(β-D-lyxofuranosyl)uracil (13a) and 6,2′-Anhydro-5-bromo-6-hydroxy-1-(β-D-lyxofuranosyl)uracil (12). Compound 11 (500 mg, 2.05 mmol) was treated with Br_2–water in a similar manner to that described in the section of **2a** to give white needles (**13a**; 387 mg, 47%): mp 197–201 °C; TLC [$CHCl_3$–EtOH (4:1)] R_f 0.67.

Anal. Calcd for $C_9H_8N_2O_6Br_2$: C, 27.03; H, 2.02; N, 7.00. Found: C, 27.42; H, 1.80; N, 6.84.

Colorless prisms (**12**; 171 mg, 28%) were obtained by treatment of the filtrate of **13a**: mp 210–212 °C; TLC [$CHCl_3$–EtOH (4:1)] R_f 0.27; UV (0.1 N HCl) λ_{max} 266.5 nm (ε 13 200); UV (H_2O, neutral) λ_{max} 266 nm (ε 13 200); UV (0.1 N NaOH) λ_{max} 265.5 nm (ε 9500).

Anal. Calcd for $C_9H_9N_2O_6Br$: C, 33.66; H, 2.83; N, 8.72. Found: C, 33.71; H, 2.52; N, 8.54.

5-Iodo-1-(5′-deoxy-β-D-lyxofuranosyl)uracil (14b). To a mixture solvent of 1 N HNO_3 (20 mL) and $CHCl_3$ (10 mL) were added 1-(5′-deoxy-β-D-lyxofuranosyl)uracil[15] (**14a**; 2.00 g) and I_2 (3.00 g). The mixture was treated in a similar manner to that described in the section of **10b** to give colorless prisms (2.53 g, 81%): mp 185–191 °C; TLC [$CHCl_3$–EtOH (9:1)] R_f 0.29; UV (0.1 N HCl) λ_{max} 287 nm (ε 7600); UV (H_2O, neutral) λ_{max} 287.5 nm (ε 7700); UV (0.1 N NaOH) λ_{max} 280 nm (ε 6000).

Anal. Calcd for $C_9H_{11}N_2O_5I$: 30.53; H, 3.13; N, 7.91. Found: C, 30.22; H, 2.86; N, 7.62.

6,2′-Anhydro-6-hydroxy-1-(5′-deoxy-β-D-lyxofuranosyl)-uracil (15). A solution of **14b** (2.53 g, 7.09 mmol) in 1 N NaOMe (71 mL) was heated under reflux for 4 h. After cooling, the mixture was concentrated to 20 mL and added with water (80 mL). The aqueous solution was treated in a similar manner to that described in the section of **11** to deposit white needles (1.37 g, 85%): mp 259–261 °C; TLC [$CHCl_3$–EtOH (4:1)] R_f 0.29; UV (0.1 N HCl) λ_{max} 251 nm (ε 16 200); UV (H_2O, neutral) λ_{max} 251 nm (ε 16 200); UV (0.1 N NaOH) λ_{max} 254 nm (ε 11 500).

(15) Fecker, R.; Codington, J.; Fox, J. J. *J. Am. Chem. Soc.* **1961**, *83*, 1889.

Anal. Calcd for $C_9H_{10}N_2O_5$: C, 47.79; H, 4.46; N, 12.39. Found: C, 48.16; H, 4.53; N, 12.52.

6,2′:6,3′-Dianhydro-5,5-dibromo-5,6-dihydro-6,6-dihydroxy-1-(5′-deoxy-β-D-lyxofuranosyl)uracil (16). A solution of **15** (226 mg, 1 mmol) and NBS (409 mg, 2.3 mmol) in DMF (3 mL) was stirred at room temperature for 3 h. The mixture was evaporated to dryness in vacuo and the residue was dissolved in CH_2Cl_2 (15 mL). The organic layer was washed with saturated $NaHCO_3$ (5 mL) and water (5 mL), dried over $MgSO_4$, and evaporated to dryness. The residue was triturated with water to give white needles (144 mg, 38%): mp 175.5–177 °C; TLC [$CHCl_3$–EtOH (9:1)] R_f 0.63.

Anal. Calcd for $C_9H_8N_2O_5Br_2$: C, 28.15; H, 2.10; N, 7.30. Found: C, 28.00; H, 1.86; N, 7.20.

5-Chloro-6,2′-O-cyclouridine (2b). To a solution of **1a** (121 mg, 0.5 mmol) in DMF (3 mL) was added NCS (113 mg, 1 mmol). The mixture was stirred in an atmosphere of argon at room temperature for 1 day and purified by the repeated (three times) preparative TLC, using the solvent of $CHCl_3$–EtOH (10:1) to afford white prisms (32 mg, 23%): mp 275–278 °C; TLC [$CHCl_3$–EtOH (10:1)] R_f 0.26; UV (0.1 N HCl) λ_{max} 264 nm (ε 13 900); UV (H_2O, neutral) λ_{max} 264 nm (ε 13 900); UV (0.1 N NaOH) λ_{max} 264 nm (ε 10 800).

Anal. Calcd for $C_9H_9N_2O_6Cl$: C, 39.08; H, 3.28; N, 10.13. Found: C, 39.08; H, 3.21; N, 9.92.

6,2′:6,5′-Dianhydro-1-(β-D-arabinofuranosyl)-5,5-dichloro-5,6-dihydro-6,6-dihydroxyuracil (3b). A solution of **1a** (840 mg, 3.47 mmol) and NCS (1.40 g, 3 equiv) in DMF (10 mL) was stirred in an atmosphere of argon at 50 °C overnight. The mixture was evaporated to dryness and the syrup was triturated with water (30 mL) to give white needles (1.03 g, 95%): mp >300 °C; TLC [$CHCl_3$–EtOH (5:1)] R_f 0.61.

Anal. Calcd for $C_9H_8N_2O_6Cl_2$: C, 34.75; H, 2.59; N, 9.01. Found: C, 35.14; H, 2.43; N, 8.85.

5-Chloro-6,3′-O-cyclouridine (6b). Compound **5** (121 mg, 0.5 mmol) was treated with NCS (100 mg, 0.75 mmol) in a similar manner to that described in the section of **2b** to give a crude solid. The product was recrystallized from H_2O (5 mL) to yield white prisms (36 mg, 29%): mp 268–272 °C; TLC [$CHCl_3$–EtOH (10:1)] R_f 0.35; UV (0.05 N HCl) λ_{max} 273 nm; UV (0.05 N NaOH) λ_{max} 273 nm.

6,3′:6,5′-Dianhydro-5,5-dichloro-5,6-dihydro-6,6-dihydroxy-1-(β-D-xylofuranosyl)uracil (7b). A mixture of **5** (840 mg, 3.47 mmol) and NCS (1.40 g, 3 equiv) in DMF (10 mL) was treated in a similar manner to that described in the section of **3b** to deposit white needles (1.01 g, 94%): mp 243–245 °C; TLC [$CHCl_3$–EtOH (5:1)] R_f 0.64.

Anal. Calcd for $C_9H_8N_2O_6Cl_2 \cdot {}^1/_2H_2O$: C, 33.77; H, 2.83; N, 8.75. Found: C, 33.70; H, 2.70; N, 8.84.

6,2′:6,5′-Dianhydro-5,5-dichloro-5,6-dihydro-6,6-dihydroxy-1-(β-D-lyxofuranosyl)uracil (13b). A mixture of **11** (242 mg, 1 mmol) and NCS (400 mg, 3 equiv) in DMF (5 mL) was stirred at 50 °C in an atmosphere of argon overnight. After cooling, the solution was evaporated to dryness and the residue was dissolved in a mixture of AcOEt (50 mL) and H_2O (10 mL). The organic layer was washed twice with water (10 mL), dried over $MgSO_4$, and evaporated. The solid was recrystallized from water to give white crystallines (210 mg, 68%): mp 253–255 °C; TLC [$CHCl_3$–EtOH (9:1)] R_f 0.44.

Anal. Calcd for $C_9H_8N_2O_6Cl_2$: C, 34.75; H, 2.59; N, 9.01. Found: C, 34.43; H, 2.44; N, 9.08.

5-Iodo-6,2′-O-cyclouridine (2c). To a solution of **1a** (245 mg, 1.01 mmol) in a mixture of AcOH (8.4 mL) and water (3.5 mL) were added I_2 (315 mg), HIO_3 (189 mg), and CCl_4 (2.1 mL). The mixture was stirred vigorously at room temperature for 1 h to give crystallines (105 mg). The filtrate was diluted with water (40 mL) and the aqueous layer was washed twice with $CHCl_3$ (5 mL). Evaporation of the solvent gave a syrup, which was triturated with EtOH (5 mL) to give white prisms (189 mg). The product was combined with the above-described crystallines, and they were recrystallized from EtOH–water to give colorless prisms (264 mg, 71%): mp 258–260 °C (lit.[10b] mp 255 °C); PC (solvent A) R_f 0.62 and (solvent B) R_f 0.43; UV (0.1 N HCl) λ_{max} 265 nm (ε 14 900); UV (H_2O, neutral) λ_{max} 266 nm (ε 14 900); UV (0.1 N NaOH) λ_{max} 263.5 (ε 11 800).

Anal. Calcd for $C_9H_9N_2O_6I$: C, 29.37; H, 2.46; N, 7.61. Found: C, 29.19; H, 2.32; N, 7.64.

5-Iodo-6,3′-O-cyclouridine (6c). To a solution of **5** (175 mg, 0.72 mmol) in a mixture solution of AcOH (6 mL) and water (2.5 mL) were added I_2 (225 mg), HIO_3 (135 mg), and CCl_4 (1.5 mL). The mixture was treated in a similar manner to that described in the section of **2c** to give pale brownish prisms (96 mg, 36%): mp 241 °C; PC (solvent A) R_f 0.64 and (solvent B) R_f 0.46; UV (0.1 N HCl) λ_{max} 273.5 nm (ε 10 300); UV (H_2O, neutral) λ_{max} 274 nm (ε 10 100); UV (0.1 N NaOH) λ_{max} 270.5 nm (ε 8300).

Anal. Calcd for $C_9H_9N_2O_6I$: C, 29.37; H, 2.47; N, 7.61. Found: C, 29.71; H, 2.44; N, 7.59.

5-Bromo-6,5′-O-cyclouridine (9a). To a solution of **8**[4] (242 mg, 1 mmol) in DMF (5 mL) was added NBS (214 mg, 1.2 mmol). The mixture was stirred at room temperature for 30 min and evaporated to a syrup. The residue was triturated with water (5 mL) to deposit crystals. Recrystallization of the product from EtOH–water gave white needles (245 mg, 76%): mp >300 °C (colored at 170 °C); TLC [$CHCl_3$–EtOH (5:1)] R_f 0.58; UV (0.1 N HCl) λ_{max} 278 nm (ε 11 300); UV (H_2O, neutral) λ_{max} 278 nm (ε 11 300); UV (0.1 N NaOH) λ_{max} 277 nm (ε 8400).

Anal. Calcd for $C_9H_9N_2O_6Br$: C, 33.67; H, 2.83; N, 8.72. Found: C, 33.70; H, 2.67; N, 8.50.

5-Chloro-6,5′-O-cyclouridine (9b). A mixture of **8** (242 mg, 1 mmol) and NCS (200 mg, 1.5 mmol) in DMF (10 mL) was stirred at 50 °C for 1 day. After cooling, the solvent was evaporated in vacuo and the residue was recrystallized from water (5 mL) to give white plates (202 mg, 55%): mp >300 °C; TLC [$CHCl_3$–EtOH (5:1)] R_f 0.28; UV (0.1 N HCl) λ_{max} 276.5 nm (ε 11 500); UV (H_2O, neutral) λ_{max} 276.5 nm (ε 11 400); UV (0.1 N NaOH) λ_{max} 276.5 nm (ε 8600).

Anal. Calcd for $C_9H_9N_2O_6Cl$: C, 39.08; H, 3.28; N, 10.13. Found: C, 38.84; H, 3.04; N, 10.03.

5-Iodo-6,5′-O-cyclouridine (9c). To a solution of **8** (242 mg, 1 mmol) in DMF (5 mL) was added NIS (270 mg, 1.2 equiv). The mixture was stirred at 50 °C for 1 h and evaporated in vacuo to a syrup. The residue was recrystallized from an aqueous EtOH to deposit white needles (304 mg, 83%): mp 238–244 °C; TLC [$CHCl_3$–EtOH (5:1)] R_f 0.61; UV (0.1 N HCl) λ_{max} 281 nm (ε 9200); UV (H_2O, neutral) λ_{max} 281 nm (ε 9100); UV (0.1 N NaOH) λ_{max} 276 nm (ε 7300).

Anal. Calcd for $C_9H_9N_2O_6I$: C, 29.37; H, 2.46; N, 7.61. Found: C, 29.71; H, 2.43; N, 7.47.

Registry No. **1a**, 17245-47-5; **1b**, 24704-29-8; **2a**, 59996-44-0; **2b**, 86197-32-2; **2c**, 17684-97-8; **3a**, 77050-08-9; **3b**, 86197-33-3; **5**, 73556-48-6; **6a**, 86197-27-5; **6b**, 86197-34-4; **6c**, 77061-97-3; **7a**, 77050-09-0; **7b**, 86197-35-5; **8**, 15425-10-2; **9a**, 77050-11-4; **9b**, 86197-36-6; **9c**, 77050-10-3; **10a**, 4348-61-2; **10b**, 86258-61-9; **11**, 86258-60-8; **12**, 86258-63-1; **13a**, 86258-62-0; **13b**, 86258-64-2; **14a**, 86197-29-7; **14b**, 86197-28-6; **15**, 86197-30-0; **16**, 86197-31-1.